

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07F 9/6584, A61K 31/675	A1	(11) International Publication Number: WO 93/05054 (43) International Publication Date: 18 March 1993 (18.03.93)
<p>(21) International Application Number: PCT/EP92/01768</p> <p>(22) International Filing Date: 4 August 1992 (04.08.92)</p> <p>(30) Priority data: MI91A002411 12 September 1991 (12.09.91) IT</p> <p>(71) Applicant (for all designated States except US): BOEHRINGER MANNHEIM ITALIA S.P.A. [IT/IT]; Via S. Uguzzone, 5, I-20126 Milano (IT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : SPINELLI, Silvano [IT/IT]; LIVI, Valeria [IT/IT]; MENTA, Ernesto [IT/IT]; Via S. Uguzzone, 5, I-20126 Milano (IT).</p> <p>(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).</p>		<p>(81) Designated States: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: OXAZAPHOSPHORINES USEFUL AS ANTITUMOR AGENTS, A PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM</p>		
<div style="text-align: center;"> </div> <div style="text-align: right; margin-top: 20px;"> (I) </div>		
<p>(57) Abstract</p> <p>Compounds of formula (I) wherein R, R₁, R₂, R_a and R_b have the meanings as defined in the disclosure, are useful as antitumor drugs.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MN	Mongolia
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Faso	GN	Guinea	NO	Norway
BG	Bulgaria	GR	Greece	NZ	New Zealand
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	PT	Portugal
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovak Republic
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CS	Czechoslovakia	LU	Luxembourg	SU	Soviet Union
CZ	Czech Republic	MC	Monaco	TD	Chad
DE	Germany	MG	Madagascar	TG	Togo
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain			US	United States of America

OXAZAPHOSPHORINES USEFUL AS ANTITUMOR AGENTS, A PROCESS
FOR THE PREPARATION THEREOF AND PHARMACEUTICAL
COMPOSITIONS CONTAINING THEM

The present invention relates to novel oxazaphosphorines having antitumor activity, to a process for the preparation thereof and to pharmaceutical compositions containing them.

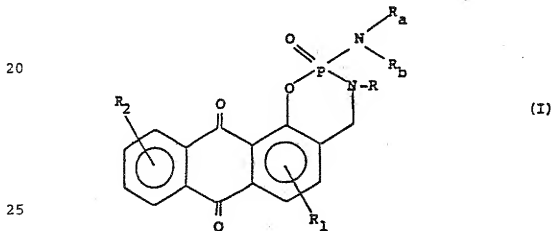
5 Cyclophosphamide is one of the most used antitumor drugs, thanks to the wide activity spectrum, in the treatment of both leukemias and solid tumors. The metabolic activation by hepatic microsomes is considered to be the first event acting in the action mechanism of
10 such a substance, and the phosphoramidate mustard, which is generated together with acrolein as a consequence of said activation, is thought to be the chemical species responsible for the cytotoxic activity of cyclophosphamide. However, this drug has undesired side-effects:
15 toxicity on urinary system, myelosuppression and immunodepression, which are partially related to acrolein formed during the activation, are frequently observed in patients treated with cyclophosphamide, and they remarkably restrict the use thereof. Moreover, resistance phenomena often occurs, as a consequence of a
20 repeated treatment.

Therefore, cyclophosphamide analogues capable of overcoming said problems are highly required. For example, in J. Med. Chem. (1991), 34, 588 phosphoramidate mustard benzyl esters are described, which release
25 the cytotoxic species through a bio-oxidative activation, without the concomitant acrolein production.

Moreover, phosphoramidate mustard nitrobenzyl esters and the corresponding heteroaromatic analogues thereof are known, which are capable of releasing the alkylating species in a reductive medium (WO 89/11484). No *in vivo* antitumor activities have been reported for the above cited substances.

The present invention relates to oxazaphosphorines, useful as antitumor agents, which can generate the alkylating species by metabolic activation, without the concomitant acrolein production. A characteristic of the compounds of the invention resides in the metabolic activation mechanism which can be of the bio-reductive kind, instead of the bio-oxidative one which is operating with the known oxazaphosphorines.

Therefore, the present invention provides 2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorines of formula (I)



wherein:

R is hydrogen, C₁-C₄ alkyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2-mesyloxyethyl;

30 R_a, R_b, which can be the same or different, are hydrogen, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2-mesy-

loxyethyl;

R_1 and R_2 , which can be the same or different, are hydrogen, C_1-C_4 alkoxy, allyloxy, propargyloxy or a group of formula $-O-(CH_2)_n-N-R_3$;

5

 R_4

R_3 and R_4 are C_1-C_4 alkyl, or together with the nitrogen atom which they are linked to, form a 5-6 membered heterocyclic ring optionally containing one or more O, N or S atoms;

10

n is an integer from 2 to 5.

The present invention also relates to the pharmaceutically acceptable salts of compounds of general formula (I), such as the addition salts with inorganic acids (hydrochloride, hydrobromide, sulfate, hydrogen sulfate, nitrate) or organic (formate, acetate, trifluoroacetate, maleate, fumarate, tartrate, methane-sulfonate, benzenesulfonate, toluenesulfonate). The present invention also relates to the racemate, the single diastereoisomers and the optically active forms of the compounds of general formula (I).

20

In general formula (I) it is understood that the R_1 and R_2 substituents can be at any one of the 5,6,8,9,10 or 11 positions of the 2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine ring.

25

In compounds of formula (I), C_1-C_4 alkyl includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl; particularly preferred are methyl and ethyl.

30

C_1-C_4 alkoxy includes methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy; particularly preferred is methoxy.

R is preferably hydrogen, 2-chloroethyl, 2-mesyloxyethyl; compounds particularly preferred are those wherein R is hydrogen.

R_a and R_b are preferably both 2-chloroethyl.

- 5 R_1 and R_2 are preferably at the 6- and 11- positions of the 2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine ring. Preferably one of R_1 or R_2 is hydrogen and the other is as defined above.

- 10 When R_3 and R_4 , taken together with the nitrogen atom which they are linked to, form a 5-6 membered heterocyclic ring, this is preferably a morpholino, pyrrolidino, piperidino, N-methylpiperazino, thiomorpholino ring; particularly preferred is the morpholino ring.

- 15 n is preferably the integer 2 or 3.

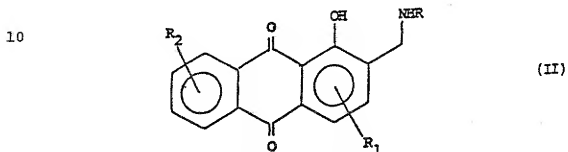
Examples of compounds of the present invention are:

- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-methoxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 20 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-allyloxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-methoxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 25 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-allyloxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(4'-morpholinyl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 30

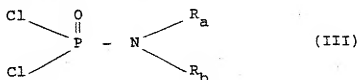
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[3-(4'-morpholinyl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(N,N-dimethylamino)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[3-(N,N-dimethylamino)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[2-(4'-morpholinyl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[2-(4'-morpholinyl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[2-(N,N-dimethylamino)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(1'-piperidyl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[3-(1'-piperidyl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[2-(4'-methylpiperazin-1'-yl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[4-(4'-methylpiperazin-1'-yl)butoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[4-(1'-

- pirrolidinyl)butoxy]-2,7,12-trioxoanthracene[2,1-e]-
 1,3,2-oxazaphosphorine;
 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[2-(1'-
 pirrolidinyl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-
 1,3,2-oxazaphosphorine.

The compounds of the invention can be prepared by reacting a compound of formula (II), optionally in form of the inorganic or organic acid addition salt,



- 15 with a compound of formula (III)



- 20 wherein R, R_a , R_b , R_1 and R_2 have the above defined meanings.

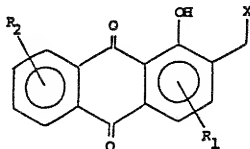
- 25 The reaction is generally carried out in an inert organic solvent, such as tetrahydrofuran, dioxane, acetonitrile, chloroform, dichloromethane, ethyl ether or mixtures thereof, in the presence of an organic base such as triethylamine, tributylamine, N-ethyl-diisopropylamine, pyridine, a N-alkylpyridine such as 2-, 3- or 4-picoline and the like or in the presence of an inorganic base such as sodium bicarbonate, potassium carbonate and the like.

- 30 The reaction can be carried out at a temperature varying from -40°C to the room temperature; the

reaction time reaction ranges from 8 to 48 hours, but generally the reaction is completed within 24 hours at room temperature.

The compounds of formula (III) are known or they can be prepared according to known methods, such as those described in: J. Am. Chem. Soc. (1954), 76, 655; J. Pharm. Sci. (1982), 71, 308; Arch. Pharm. (1982), 315, 577; Arch. Pharm. (1981), 314, 85; J. Am. Chem. Soc. (1979), 101, 7712.

The compounds of general formula (II) can be prepared from the compounds of formula (IV)

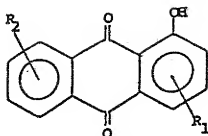


(IV)

wherein R₁ and R₂ are as defined above and X is a leaving group such as chlorine, bromine, iodine, mesyloxy or tosyloxy, by reaction with a compound of formula R-NH₂, wherein R is as defined above.

An alternative method, which can advantageously be used for the preparation of the compounds of formula (II) wherein R is hydrogen, consists in reacting compounds of formula (IV) with hexamethylenetetramine and subsequent acid hydrolysis of the obtained hexamethylenetetrammonium salt according to known procedures (see for instance Org. Reac. vol. 8 chapt. 4).

The compounds of formula (IV) can be prepared by a multi-step process, which comprises Marschalk hydroxymethylation of the compounds of formula (V)



(V)

5

and subsequent functionalization of the obtained benzyl alcohol by means of halogenation or mesylation reactions and the like, according to what is described, for example, in: Chem. Ber. (1980), 113, 306; Chem. Pharm. Bull. (1989), 37, 3294; Liebigs Ann. Chem. (1979), 19; Liebigs Ann. Chem. (1984), 306; Phytochemistry (1981), 20, 2441.

The compound of formula (V) wherein R_1 and R_2 are both hydrogen is known and commercially available.

15 The compounds of formula (V) wherein one of R_1 or R_2 is different from hydrogen and the other is hydrogen are known or they can be prepared from the corresponding dihydroxyanthraquinones (which are known or commercially available) by monoalkylation with a compound of formula R_5-X wherein R_5 is a C_1-C_4 alkyl,

allyl or propargyl or a group of formula $-(CH_2)_n-\overset{\overset{R_4}{|}}{N}-R_3$ being X, n, R_3 and R_4 as defined above. Useful teachings to carry out the monoalkylation can be found in: Liebigs Ann. Chem. (1978), 2018; Liebigs Ann. Chem. (1984), 306; Tetrahedron Lett. (1984), 25, 803; Chem. Ber. (1980), 113, 2994; Liebigs Ann. Chem. (1980), 814. Alternatively, the compounds of formula (V) wherein R_1 or R_2 are the $-O-(CH_2)_n-\overset{\overset{R_4}{|}}{N}-R_3$ group, can be prepared by

30

monoalkylation of the corresponding dihydroxyanthraqui-

nones with a compound of formula $X'-(CH_2)_n-Cl$, wherein X' is chlorine, bromine, iodine but preferably bromine or iodine and n is as defined above, and subsequent reaction of the obtained compound with the amine of

5 formula $HN-R_3$.



The compounds of the invention have a marked cytotoxic activity on tumor cells, as it can be evidenced by the in vitro tests carried out for example,

10 according to the procedure described by W.R. Wilson and W.A. Danny, Brit. J. Cancer. 49, 215 (1984). The IC_{50} s (i.e. the substance concentrations capable of inhibiting by 50% the growth of tumor cells, compared with controls) under aerobic (air IC_{50}) and anaerobic

15 (nitrogen IC_{50}) conditions and the hypoxic selectivity factor, by the air IC_{50} /nitrogen IC_{50} ratio have been determined for the compounds of the invention.

The hypoxic selectivity is evidenced by values of the hypoxic selective factor which are significantly

20 higher than 1. The cell lines used in these experiments are AA8 (Mutat. Res., (1980), 74, 21) and a mutant line thereof, UV4, which lacks the DNA-repair mechanisms from damages caused by alkylating agents. Said cell lines can be grown either in monolayer or in

25 suspension, as described by Whillans and Rauth, Radiat. Res., (1980), 34, 97. A representative compound of the present invention, 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-methoxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine, proved to have a hypoxic

30 selectivity factor of 1.3 in the AA8 cell line and of 2.6 in the UV4 cell line, thus proving that the

bio-reductive activation preferentially occurs in the hypoxic cells of tumor tissues, which are generally resistant to chemotherapy and radiotherapy. Therefore, in consideration of the property to be selective by cytotoxic to hypoxic environment, the compounds of the present invention have a good toxicity profile. Moreover, the compounds of the invention have potentially no cross-resistance with cyclophosphamide, since they have an activation mechanism different from the one of cyclophosphamide. The compounds of formula (I), when administered to men and animals bearing tumors which can be treated with alkylating agents, at doses ranging from 1 to 1200 mg/m² body area, are capable of inducing the regression of said tumors.

The effective dosage of the compounds of the invention can be determined by the expert clinician with conventional methods. The relationship between the dosages used for animals of various species and those for humans (on the basis of mg/m² body area) is described by Freireich, E.J., et al., Cancer Chemoter. Rep., 50, n.4, 219-244, May 1966. In particular, solid tumors such as lung, mammary, prostate carcinomas, colo-rectal tumors, as well as circulating neoplasia, such as lymphoid leukemia can be advantageously treated.

The compounds of the invention can be administered by the parenteral route (intravenously, intramuscularly, intraarterially, intraperitoneally) in form of sterile aqueous solutions or sterile powders for the extemporaneous preparation of solutions, oily preparations for the intramuscular or intraperitoneal administrations.

The compounds of the invention can also be administered by the oral route: in this case, useful pharmaceutical forms can be solid, such as tablets or capsules, which can optionally be gastro-resistant, or
5 liquid, such as syrups and the like.

The following examples further illustrate the invention.

EXAMPLE 1

1-Chloro-3-iodopropane (20.1 ml) is dropped into a
10 solution heated to 60°C of 1-acetoxy-8-hydroxyanthraquinone (Liebigs Ann. Chem. (1984) 306) (28 g) in dimethylformamide (DMF; 800 ml), containing potassium carbonate (K_2CO_3 ; 34.6 g) as insoluble, with stirring. The resulting mixture is stirred at 60°C for 6 hours ,
15 then it is poured into ice-water (1.5 l). A precipitate separates which is filtered and washed with water.

After drying in oven under vacuum at 40°C, 35 g of 1-acetoxy-8-(3-chloropropoxy)anthraquinone as a yellow solid are obtained, m.p.= 157°-158°C.

20 1H -NMR ($CDCl_3$, TMS): δ = 2.37 (m, 2H); 2.5 (s, 3H); 3.97 (t, 3H); 4.3 (t, 3H); 7.35 (dd, 1H); 7.4 (dd, 1H); 7.7 (m, 2H); 7.9 (dd, 1H); 8.2 (dd, 2H).

EXAMPLE 2

A solution of 1-chloro-3-iodopropane (24.2 ml) in
25 DMF (20 ml) is added dropwise to a solution heated to 60°C of quinizarin (1,4-dihydroxyanthraquinone; 30 g) in DMF (450 ml), containing K_2CO_3 (32.6 g) as insoluble, under stirring, during 3 hours. The resulting mixture is stirred at 60°C for 24 hours, and
30 subsequently is cooled to room temperature and partitioned between water (400 ml) and dichloromethane (300

ml). The aqueous phase is reextracted with dichloromethane (2 x 200 ml) and the combined extracts are dried (Na_2SO_4) and evaporated to dryness. The resulting crude product is purified by silica gel chromatography (eluant dichloromethane/hexane 8:2) to give 14 g of 1-hydroxy-4-(3-chloropropoxy)anthraquinone as an orange solid, m.p. = 138°-143°C.

$^1\text{H-NMR}$ (CDCl_3 , TMS): δ = 2.35 (m, 2H); 3.98 (t, 2H); 4.3 (t, 2H); 7.3 (dd, 1H); 7.4 (dd, 1H); 7.77 (m, 2H); 8.25 (m, 2H); 13.0 (s, 1H).

EXAMPLE 3

Using in the procedures described in examples 1 and 2 the appropriate ω -chloroalkyl iodides or tosylates, the following compounds were prepared:

1-acetoxy-8-(2-chloroethoxy)anthraquinone;
1-acetoxy-8-(4-chlorobutoxy)anthraquinone;
1-hydroxy-4-(2-chloroethoxy)anthraquinone;
1-hydroxy-4-(4-chlorobutoxy)anthraquinone.

EXAMPLE 4

To a solution of 1-acetoxy-8-(3-chloropropoxy)anthraquinone (4.5 g) in DMF (140 ml), NaHCO_3 (5.2 g) and KI (4.2 g) as insoluble are added with stirring, followed by morpholine (3.3 ml). The resulting mixture is heated to 80°C for 8 hours, then it is allowed to cool to room temperature and it is poured into 2N hydrochloric acid (150 ml). The obtained solution is extracted with ethyl acetate (3 x 30 ml) and the organic extracts are discarded. The acid solution is alkalized to pH 8 by adding 35% NaOH and the resulting mixture is extracted with ethyl acetate (3 x 100 ml); the combined organic extracts are washed with

water (100 ml), dried (Na_2SO_4) and concentrated to small volume. A solution of anhydrous hydrochloric acid in absolute ethanol (6.7N; 3 ml) is dropped into the obtained solution, cooled with ice-bath, under nitrogen atmosphere and with stirring, A precipitate separates which is filtered and recrystallized from methanol to give 3.5 g of 1-hydroxy-8-[3-(4'-morpholinyl)propoxy]anthraquinone hydrochloride as a yellow solid, m.p. = 245°-246°C (with dec.).

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$, TMS): δ = 2.3 (m, 2H); 3.15 (m, 2H); 3.5 (m, 4H); 3.9 (m, 4H); 4.3 (t, 2H); 7.36 (dd, 1H); 7.75 (m, 5H); 12.9 (s, 1H).

EXAMPLE 5

Following the procedure described in example 4, by reacting ω -chloroalkoxyanthraquinones prepared in examples 1, 2 and 3 with the appropriate amines, the following compounds were prepared as the hydrochloride salts:

1-hydroxy-4-[3-(4'-morpholinyl)propoxy]anthraquinone
m.p. = 212°-216°C (with dec.).
 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, TMS): δ = 2.28 (m, 2H); 3.15 (m, 2H); 3.5 (m, 4H); 3.9 (m, 4H); 4.25 (t, 2H); 7.45 (s, 1H); 7.95 (m, 2H); 8.2 (m, 2H); 10.85 (s, all., 1H); 12.8 (s, 1H).

1-hydroxy-8-[2-(4'-morpholinyl)ethoxy]anthraquinone;
1-hydroxy-4-[2-(4'-morpholinyl)ethoxy]anthraquinone;
1-hydroxy-8-[3-(N,N-dimethylamino)propoxy]anthraquinone;
1-hydroxy-8-[2-(N,N-dimethylamino)ethoxy]anthraquinone;
1-hydroxy-4-[3-(N,N-dimethylamino)propoxy]anthraquinone;
1-hydroxy-4-[2-(N,N-dimethylamino)ethoxy]anthraquinone;

1-hydroxy-8-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone;

1-hydroxy-4-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone;

5 1-hydroxy-8-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone;

1-hydroxy-4-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone.

EXAMPLE 6

10 A suspension of 1-hydroxy-8-[3-(4'-morpholinyl)propoxy]anthraquinone hydrochloride (1.6 g) in methanol (50 ml) cooled to 0°-5°C with an ice-bath, under nitrogen atmosphere and with stirring, is added dropwise with 1N NaOH (10 ml) and subsequently with a
15 solution of Na₂S₂O₄ (3.5 g) in water (35 ml).

At the end of the addition 37% formaldehyde (4.85 ml) is added in a single portion and the reaction mixture is stirred at the same temperature for 2 hours; then the reaction mixture is diluted with water (100
20 ml) and air is bubbled through for 15-30 minutes at room temperature. After adjusting pH to 7 with a NaH₂PO₄ saturated solution, a precipitate separates which is filtered, washed with water, dried under vacuum over P₂O₅ and recrystallized from ethyl
25 acetate/methanol 4:1 to give 1 g of 1-hydroxy-2-hydroxymethyl-8-[3-(4'-morpholinyl)propoxy]anthraquinone as an yellow-orange solid, m.p.= 149°-150°C.

¹H-NMR (MeOD, TMS): δ = 2.25 (m, 2H); 2.6 (m, 4H); 2.8 (t, 2H); 3.75 (m, 4H); 4.3 (t, 2H); 4.8 (s, 2H); 7.5
30 (dd, 1H); 7.8 (m, 4H).

EXAMPLE 7

Following the procedure described in example 6, 1-hydroxyanthraquinones of example 5 were transformed into the following 2-hydroxymethylanthraquinones:

- 5 1-hydroxy-2-hydroxymethyl-4-[3-(4'-morpholinyl)propoxy]anthraquinone; m.p. = 153°-156°C;
1-hydroxy-2-hydroxymethyl-8-[2-(4'-morpholinyl)ethoxy]anthraquinone;
1-hydroxy-2-hydroxymethyl-4-[2-(4'-morpholinyl)ethoxy]anthraquinone;
10 1-hydroxy-2-hydroxymethyl-8-[3-(N,N-dimethylamino)propoxy]anthraquinone;
1-hydroxy-2-hydroxymethyl-8-[2-(N,N-dimethylamino)ethoxy]anthraquinone;
15 1-hydroxy-2-hydroxymethyl-4-[3-(N,N-dimethylamino)propoxy]anthraquinone;
1-hydroxy-2-hydroxymethyl-4-[2-(N,N-dimethylamino)ethoxy]anthraquinone;
1-hydroxy-2-hydroxymethyl-8-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone;
20 1-hydroxy-2-hydroxymethyl-4-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone;
1-hydroxy-2-hydroxymethyl-8-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone;
25 1-hydroxy-2-hydroxymethyl-4-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone.

EXAMPLE 8

- Under nitrogen atmosphere thionyl chloride (0.62 ml) is added to a suspension of 1-hydroxy-2-hydroxymethyl-8-[3-(4'-morpholinyl)propoxy]anthraquinone (1.19 g) in DMF (20 ml) while cooling with an ice-
- 30

bath. The reaction mixture is left to warm to room temperature and then it is heated to 50°C for one hour. From the resulting solution, by cooling to 0°C and diluting with ethyl ether, an orange solid crystallizes which is filtered and dried under vacuum at room temperature to give 1-hydroxy-2-chloromethyl-8-[3-(4'-morpholinyl)propoxy]anthraquinone hydrochloride, m.p.= 236°-237°C (with dec.).

¹H-NMR (MeOD,TMS): δ = 2.42 (m, 2H); 3.3 (m, 2H); 3.65 (t, 2H); 3.75 (m, 4H); 3.9 (m, 2H); 4.15 (m, 2H); 4.37 (t, 2H); 4.77 (s, 2H); 7.55 (dd, 1H); 7.85 (m, 4H).

EXAMPLE 9

Following the procedure described in example 8, 2-hydroxymethylantraquinones of example 7 were transformed into the following 2-chloromethylantraquinones: 1-hydroxy-2-chloromethyl-4-[3-(4'-morpholinyl)propoxy]-anthraquinone hydrochloride; m.p.= 229°-232°C (with dec.).

1-hydroxy-2-chloromethyl-8-[2-(4'-morpholinyl)ethoxy]-anthraquinone hydrochloride;

1-hydroxy-2-chloromethyl-4-[2-(4'-morpholinyl)ethoxy]-anthraquinone hydrochloride;

1-hydroxy-2-chloromethyl-8-[3-(N,N-dimethylamino)propoxy]anthraquinone hydrochloride;

1-hydroxy-2-chloromethyl-8-[2-(N,N-dimethylamino)ethoxy]anthraquinone hydrochloride;

1-hydroxy-2-chloromethyl-4-[3-(N,N-dimethylamino)propoxy]anthraquinone hydrochloride;

1-hydroxy-2-chloromethyl-4-[2-(N,N-dimethylamino)ethoxy]anthraquinone hydrochloride;

1-hydroxy-2-chloromethyl-8-[3-(4'-methylpiperazin-1'-

- yl)propoxy]anthraquinone dihydrochloride;
1-hydroxy-2-chloromethyl-4-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone dihydrochloride;
1-hydroxy-2-chloromethyl-8-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone dihydrochloride;
1-hydroxy-2-chloromethyl-4-[2-(4'-methylpiperazin-1'-yl)ethoxy] anthraquinone dihydrochloride.

EXAMPLE 10

- 1-Hydroxy-2-chloromethyl-8-[3-(4'-morpho-
lanyl)propoxy]anthraquinone hydrochloride (400 mg) is
added in portions to a suspension of NaHCO_3 (1 g) in
chloroform (50 ml). The suspension is vigorously
stirred for 30 minutes, then it is filtered and the
solid is thoroughly with chloroform (25 ml) and finally
with methanol (5 ml). The combined filtrates are
concentrated to small volume (25 ml) and dropped in one
hour into a solution of hexamethylenetetramine (230 mg)
in chloroform (5 ml) heated to reflux. When dropping is
over, heating is continued for 6 hours. A precipitate
separates which, after cooling to a room temperature is
filtered to give 370 mg of 1-hydroxy-2-
(hexamethylenetetrammonium)methyl-8-[3-(4'-morpho-
lanyl)propoxy]anthraquinone chloride; m.p. = 184°C - 186°C
(with dec.).
 $^1\text{H-NMR}$ (MeOD, TMS): δ = 2.35 (m, 2H); 3.15 (m, 4H); 3.35
(m, 2H); 3.9 (m, 4H); 4.2 (s, 2H); 4.37 (t, 2H); 4.65
(m, 6H); 5.25 (s, 6H); 7.6 (dd, 1H); 7.9 (m, 4H).

EXAMPLE 11

- Following the procedure described in example 10,
by reacting 2-chloromethylanthraquinones prepared in
example 9 with hexamethylenetetramine, the following

compounds were obtained: 1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-[3-(4'-morpholinyl)propoxy]anthraquinone chloride; m.p. = 189°-191°C (with dec.);

- 5 1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-[2-(4'-morpholinyl)ethoxy]anthraquinone chloride;
1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-[2-(4'-morpholinyl)ethoxy]anthraquinone chloride;
1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-[3-(N,N-dimethylamino)propoxy]anthraquinone chloride;
10 1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-[2-(N,N-dimethylamino)ethoxy]anthraquinone chloride;
1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-[3-(N,N-dimethylamino)propoxy]anthraquinone chloride;
15 1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-[2-(N,N-dimethylamino)ethoxy]anthraquinone chloride;
1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone chloride;
1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-[3-(4'-methylpiperazin-1'-yl)propoxy]anthraquinone chloride;
20 1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone chloride;
1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-[2-(4'-methylpiperazin-1'-yl)ethoxy]anthraquinone chloride.

25

EXAMPLE 12

- A solution of 1-hydroxy-2-chloromethyl-4-methoxyanthraquinone [prepared according to the procedure described in Chem. Ber. (1980), 113, 2994-3009], (500 mg) in CHCl_3 (20 ml), is dropped during one
30 hour into a refluxing solution of hexamethylenetetramine (700 mg) in chloroform (5 ml).

After that, heating is continued for 6 hours. A precipitate separates which, after cooling to room temperature, is filtered, washed with ethyl ether and dried under vacuum to give 570 mg of 1-hydroxy-2-(hexamethylenetetrammonium)methyl-4-methoxy-anthraquinone chloride as a red solid, m.p. = 201°-205°C.

¹H-NMR (MeOD, TMS); δ = 4.05 (s, 3H); 4.2 (s, 2H); 4.65 (m, 6H); 5.3 (s, 6H); 7.75 (s, 1H); 7.9 (m, 2H); 8.25 (m, 2H).

Analogously, using 1-hydroxy-2-chloromethyl-8-methoxyanthraquinone [prepared according to the procedure described in Liebigs Ann. Chem. (1984), 306-318] as the starting compound, 1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-methoxyanthraquinone chloride is obtained, m.p. 184-186°C.

¹H-NMR (D₃OD, TMS); δ = 2.35 (m, 2H); 3.18 (m, 4H); 3.30 (t, 2H); 3.90 (m, 4H); 4.20 (s, 2H); 4.30 (t, 2H); 4.65 (q, 6H); 5.25 (s, 6H); 7.60 (dd, 1H); 7.90 (m, 4H).

EXAMPLE 13

Concentrated hydrochloric acid (0.45 ml) is added to a solution of 1-hydroxy-2-(hexamethylenetetrammonium)methyl-8-[3-(4'-morpholinyl)propoxy]anthraquinone chloride (370 mg) in water (0.45 ml) and the mixture is stirred at room temperature for 16 hours. An orange solid separates, which is filtered, washed with tetrahydrofuran and dried under vacuum, to give 300 mg of 1-hydroxy-2-aminomethyl-8-[3-(4'-morpholinyl)propoxy]anthraquinone dihydrochloride, m.p. = 249°-250°C (with dec.).

¹H-NMR (D₂O, TMS): δ = 2.43 (m, 2H); 3.6 (m, 6H); 4.1

(m, 4H); 4.3 (t + s; 4H); 7.4 (dd, 1H); 7.75 (m, 4H).

EXAMPLE 14

By reacting the hexamethylenetetrammonium salts described in examples 11 and 12 according to the procedure described in example 13, the following compounds were prepared:

1-hydroxy-2-aminomethyl-4-[3-(4'-morpholinyl)propoxy]-anthraquinone dihydrochloride; m.p. = 237°-238°C (with dec.).

¹H-NMR (D₂O, TMS): δ = 2.42 (m, 2H); 3.6 (m, 6H); 4.25 (m, 8H); 7.45 (s, 1H); 7.92 (m, 2H); 8.1 (m, 1H); 8.22 (m, 1H).

1-hydroxy-2-aminomethyl-4-methoxyanthraquinone hydrochloride; m.p. = 187° dec.

¹H-NMR (D₂O, TMS): δ = 3.82 (s, 3H); 4.15 (s, 2H); 7.4 (s, 1H); 7.8 (m, 4H);

1-hydroxy-2-aminomethyl-8-methoxyanthraquinone hydrochloride, m.p. 242-243°C;

1-hydroxy-2-aminomethyl-8-[2-(4'-morpholinyl)ethoxy]anthraquinone dihydrochloride;

1-hydroxy-2-aminomethyl-4-[2-(4'-morpholinyl)ethoxy]anthraquinone dihydrochloride;

1-hydroxy-2-aminomethyl-8-[3-(N,N-dimethylamino)propoxy]anthraquinone dihydrochloride;

1-hydroxy-2-aminomethyl-8-[2-(N,N-dimethylamino)ethoxy]anthraquinone dihydrochloride;

1-hydroxy-2-aminomethyl-4-[3-(N,N-dimethylamino)propoxy]anthraquinone dihydrochloride;

1-hydroxy-2-aminomethyl-4-[2-(N,N-dimethylamino)ethoxy]anthraquinone dihydrochloride;

1-hydroxy-2-aminomethyl-8-[3-(4'-methylpiperazin-1'-

yl)propoxy]anthraquinone trihydrochloride;
1-hydroxy-2-aminomethyl-4-[3-(4'-methylpiperazin-1'-
yl)propoxy]anthraquinone trihydrochloride;
1-hydroxy-2-aminomethyl-8-[2-(4'-methylpiperazin-1'-
5 yl)ethoxy]anthraquinone trihydrochloride;
1-hydroxy-2-aminomethyl-4-[2-(4'-methylpiperazin-1'-
yl)ethoxy]anthraquinone trihydrochloride.

EXAMPLE 15

Into a stirred suspension of 1-hydroxy-2-
10 aminomethyl-8-[3-(4'-morpholinyl)propoxy]anthraquinone
dihydrochloride (50 mg) and N,N-bis(2-
chloroethyl)phosphoramidate dichloride (30 mg) [prepared
according to the procedure described in J. Pharm. Sci.
(1982), 71, 308] in tetrahydrofuran/acetonitrile 1:1 (4
15 ml) while cooling with an ice-bath and under nitrogen
atmosphere. A solution of triethylamine (0.065 ml) in
tetrahydrofuran/acetonitrile 1:1 (1 ml) is dropped.
When the addition is over, the reaction mixture is left
to warm to room temperature and it is stirred for 16
20 hours. After dilution with chloroform (5 ml), the
organic phase is washed with water (2 x 3 ml), dried
over sodium sulfate and concentrated to small volume.
By addition of ethyl ether to the resulting solution, a
yellow solid separates, which is quickly filtered under
25 nitrogen atmosphere to give 15 mg of 3,4-dihydro-(2H)-
2-[bis(2-chloroethyl)amino]-11-[3-(4'-morpholinyl)pro-
poxyl-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazapho-
sphorine;
 $^1\text{H-NMR}$ (DMSO-d_6 .TMS): δ = 2.25 (m, 2H); 3.3 (m, 10H);
30 3.6 (m, 4H); 3.7 (t, 4H); 4.3 (t + m, 4H); 5.9 (m, 1H);
7.6 (dd, 1H); 7.8 (m, 4H).

EXAMPLE 16

By reacting 2-aminomethylanthraquinones prepared in example 14 with N,N-bis(2-chloroethyl)phosphoramid dichloride according to the procedure described in example 15, the following compounds were prepared:

3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(4'-morpholinyl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine.

m.p. = 176°-178°C (with dec.).

¹H-NMR (DMSO-d₆, TMS): δ = 2.0 (m, 2H); 3.3 (m, 10H); 3.6 (m, 4H); 3.7 (t, 4H); 4.15 (t, 2H); 4.3 (m, 2H); 5.9 (m, 1H); 7.6 (s, 1H); 7.85 (m, 2H); 8.1 (m, 2H).

3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-methoxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;

m.p. = 203°-204°C;

¹H-NMR (DMSO, TMS) δ = 3.35 (m, 4H); 3.75 (t, 4H); 3.95 (s, 3H); 4.32 (m, 2H); 5.90 (dt, 1H); 7.58 (dd, 1H); 7.8 (m, 4H).

3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-methoxy-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine; m.p. 210-212°C;

¹H-NMR (DMSO-d₆, TMS) δ = 3.35 (m, 4H); 3.75 (t, 4H); 3.93 (s, 3H); 4.32 (dd, 2H); 5.85 (dt, 1H); 7.61 (s, 1H); 7.86 (m, 2H); 8.07 (m, 2H).

3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[2-(4'-morpholinyl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;

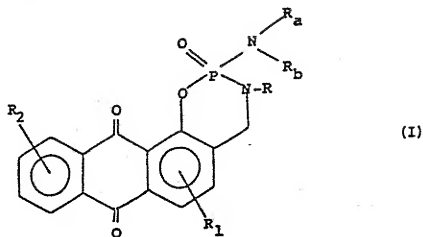
3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[2-(4'-morpholinyl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;

3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[3-

- (N,N-dimethylamino)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[2-(N,N-dimethylamino)-ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 5 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(N,N-dimethylamino)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[2-(N,N-dimethylamino)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 10 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[3-(4'-methylpiperazin-1'-yl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 15 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(4'-methylpiperazin-1'-yl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-11-[3-(4'-methylpiperazin-1'-yl)ethoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine;
- 20 3,4-dihydro-(2H)-2-[bis(2-chloroethyl)amino]-6-[3-(4'-methylpiperazin-1'-yl)propoxy]-2,7,12-trioxoanthracene[2,1-e]-1,3,2-oxazaphosphorine.

CLAIMS

1. Compounds of formula I



wherein:

R is hydrogen, C_1-C_4 alkyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2-mesyloxyethyl;

R_a , R_b , which can be the same or different, are hydrogen, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2-mesyloxyethyl;

R_1 and R_2 , which can be the same or different, are hydrogen, C_1-C_4 alkoxy, allyloxy, propargyloxy or a group of formula $-O-(CH_2)_n-N-R_3$;

R_3 and R_4 are C_1-C_4 alkyl, or taken together with the nitrogen atom which they are linked to, they form a 5-6 membered heterocyclic ring optionally containing one or more O, N or S atoms;

n is an integer from 2 to 5;

and the pharmaceutically acceptable salts thereof,

2. Compounds according to claim 1, wherein R is hydrogen, 2-chloroethyl or 2-mesyloxymethyl.

3. Compounds according to claims 1 or 2, wherein R_a

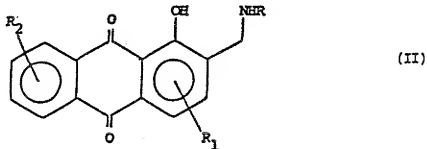
and R_D are both 2-chloroethyl.

4. Compounds according to any one of the previous claims, wherein one of R_1 and R_2 is hydrogen and the other is as defined in claim 1.

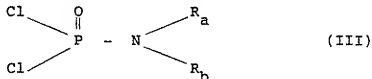
5. Compounds according to any one of the previous claims, wherein R_1 or R_2 are a group of formula $-O-(CH_2)_n-N-R_3$ in which R_3 and R_4 are C_1-C_4 alkyl, or,

taken together with the nitrogen atom, they form a morpholino, pyrrolidino, piperidino, N-methylpiperazino, thiomorpholino ring, and n is the integer 2 or 3.

6. A process for the preparation of the compounds of formula (I) characterized in that a compound of formula (II), optionally in the form of an inorganic or organic acid addition salt,



is reacted with a compound of formula (III)



wherein R , R_a , R_D , R_1 and R_2 have the above mentioned meanings.

7. Pharmaceutical compositions containing as the active ingredient a compound of claims 1-5 in admixture with a pharmaceutically acceptable carrier.

8. The use of the compounds of claims 1 to 5 for the

preparation of a medicament having antitumor activity.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01768

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 F 9/6584, A 61 K 31/675		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	C 07 F	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	J. Med. Chem., vol. 18, No. 12, December 1975, S M Ludeman et al.: "Synthesis and Antitumor Activity of Cyclophosphamide Analogs. I. Benzo Annulated Cyclophosphamide and Related Systems ", see page 1251 - page 1253 see compound 2 ---	1-8
A	GB, A, 812651 (ASTA-WERKE A.G.) 29 April 1959, see example 12 ---	1-8
A	J. Med. Chem., vol. 34, No. 2, February 1991, Chul-Hoon Kwon et al.: "Chemically Stable, Lipophilic Prodrugs of Phosphoramidate Mustard as Potential Anticancer Agents ", see page 588 - page 592 ---	1-8
<p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
5th November 1992	03 DEC 1992	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	Göran Karlsson	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)	
Category *	Relevant to Claim No
A	WO, A1, 8911484 (RESEARCH CORPORATION TECHNOLOGIES, INC.) 30 November 1989, see the whole document

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/EP 92/01768**

SA 63767

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/09/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 812651	29/04/59	BE-A- 554888	00/00/00
		BE-A- 563332	00/00/00
		CH-A- 361279	00/00/00
		CH-A- 369451	00/00/00
		CH-A- 370406	00/00/00
		DE-B- 1054997	00/00/00
		DE-B- 1057119	00/00/00
		DE-B- 1116672	00/00/00
		FR-E- 75178	00/00/00
		FR-E- 75308	00/00/00
		FR-A- 1246708	00/00/00
		GB-A- 853044	00/00/00
		NL-C- 99649	00/00/00
		NL-C- 99688	00/00/00
		US-A- 3018302	00/00/00
		US-A- 3074992	00/00/00
WO-A1- 8911484	30/11/89	EP-A- 0418292	27/03/91
		JP-T- 4501253	05/03/92

For more details about this annex: see Official Journal of the European Patent Office, No. 12/82